

# Solid Tumour Section

## Review

## Lung: Translocations in Small Cell Carcinoma

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### Abstract

Review on translocations in small cell carcinoma, with data on clinics, genetics and cytogenetics.

### Classification

In the group of malignant epithelial tumours of the lungs, small cell carcinomas (small cell lung cancer (SCLC)) are usually opposed to non-small cell carcinomas (non-small cell lung cancer (NSCLC)). Small cell carcinoma is a pulmonary neuroendocrine tumour.

Other neuroendocrine tumours of the lungs are large cell neuroendocrine carcinomas, typical carcinoids, and atypical carcinoids.

### Clinics and pathology

#### Disease

Lung small cell carcinoma

#### Epidemiology

Small cell carcinomas comprise about 15-20% of lung cancers.

Small cell carcinoma is more often associated with tobacco smoking than adenocarcinoma, and less than squamous cell carcinoma.

#### Clinics

Patients are typically men older than 60-70 years. Small cell carcinoma more often presents with symptoms of early metastases.

Location of the tumour is usually central, but SCLC may occur in a peripheral location.

Bronchoscopic biopsy is often positive (van Meerbeeck et al., 2011).

#### Cytology

Small round or oval cells with a finely granular nucleus and frequent mitoses.

#### Pathology

Immunohistochemistry is often positive for neuroendocrine markers, such as chromogranin, synaptophysin, and CD56; SCLCs are also positive for NKX2-1 (14q13, also called TTF-1, a tissue-specific transcription factor in lung epithelial cells) in most cases.

#### Prognosis

Although SCLC is extremely sensitive to initial chemotherapy and radiotherapy, most patients eventually relapse. SCLC is an aggressive disease with poor prognosis, with a five years survival of 5%. High expression of SOX2 (3q26) and FGFR1 (8p11) are associated with the worst outcome (Yang et al., 2013).

### Genetics

#### Note

TP53 (17p13) mutations are detected in 70 to 90% of SCLCs. RB1 (13q14) and the retinoblastoma pathway are inactivated in most SCLCs. PTEN (10q23) is mutated in 2 to 10%. MYC (8q24) amplifications and amplification of MYC family members are found in 30% of SCLCs in pre-invasive stages. Loss of heterozygosity (LOH) on chromosome arm 3p is found in more than 80% of SCLCs, including the loss of FHIT (3p14) protein expression. FHIT controls the invasive phenotype of lung cancer cells by regulating the expression of genes associated with epithelial-mesenchymal transition.

FHIT loss confers cisplatin resistance in lung cancer via the AKT/NF-KB/SLUG pathway (Wu et al., 2014). In wide genomic analyses, an elevated rate of C:G>A:T transversions were found, compared to neutral mutations, consistent with demonstrated effects of tobacco smoke carcinogens on DNA. SOX2, a transcription factor, one of the genes able to reprogram human somatic cells to pluripotent stem cells (Lin et al., 2011) was amplified in 27% of the samples. A recurrent RLF/MYCL translocation was found in 9% of SCLCs, and the RLF/MYCL fusion overexpressed MYCL (1p34). FGFR1 was amplified in 6%. Chromatin-modifying enzymes such as EP300 (22q13) were frequently mutated (Peifer et al., 2012; Rudin et al., 2012). To be noted that SOX2 and FGFR1 are also known to be implicated in a subset of squamous cell carcinoma of the lung (Pietanza and Ladanyi, 2012). In contrast with lung adenocarcinomas, there is no molecularly targeted agents yet for small cell carcinomas of the lung.

## Cytogenetics

### Note

Only a few genes have been found implicated in many different translocations:

- RLF (1p34), a zinc finger protein, which may be involved in transcriptional regulation. Depletion of Rlf leads to DNA hypermethylation in the mouse. RLF is likely to be involved in epigenetic processes (Daxinger et al., 2013), RLF is translocated with 10 different partners (herein below) in SCLCs;
- BCL2L1 (20q11) an inhibitor of cell death, involved in various cancers, translocated with 7 different partners (herein below) in SCLCs;
- PVT1 (8q24), a non-protein coding and oncofetal gene, translocated with various partners in: breast cancer, Ewing/PNET spectrum, and hematological malignancies, and with 7 different partners (herein below) in SCLCs; PVT1 is a hotspot for chromosomal breaks during MYC amplification (L'Abbate et al., 2014).
- Other genes recurrently found are HM13 (20q11), translocated with 3 different partners, and MYCL, BMP8B (1p34), CAP1 (1p34), CREBBP (16p13), and DNM2 (19p13), implicated twice each.

### Cytogenetics Morphological

Fusion transcripts were often found in amplified regions in 1p34, 2p24, 8q24, and 9p24, suggesting that amplification and fusion of genes occur simultaneously by chromothripsis (Iwakawa et al., 2013). One hundred translocations have so far been reported in small cell carcinoma of the lung. They are the following:

t(1;1)(p36;p36) RERE/SLC2A5 (Iwakawa et al., 2013)

t(1;1)(p36;p34) RLF/FAM132A (Iwakawa et al., 2013)  
 t(1;1)(p36;p34) RLF/UBE2J2 (Iwakawa et al., 2013)  
 t(1;1)(p35;p35) SERINC2/ZCCHC17 (Rudin et al., 2012)  
 inv(1)(p34p34) BMP8B/RLF (Rudin et al., 2012)  
 inv(1)(p34p34) CAP1/BMP8B (Rudin et al., 2012)  
 inv(1)(p34p34) RLF/PPT1 (Rudin et al., 2012)  
 t(1;1)(p34;p34) CAP1/MACF1 (Iwakawa et al., 2013)  
 t(1;1)(p34;p34) INPP5B/SF3A3 (Rudin et al., 2012)  
 t(1;1)(p34;p34) inv(1)(p34p34) RLF/MYCL (Rudin et al., 2012; Iwakawa et al., 2013)  
 t(1;1)(p34;p34) RLF/COL9A2 (Iwakawa et al., 2013)  
 t(1;1)(p34;p34) RLF/SMAP2 (Iwakawa et al., 2013)  
 t(1;1)(p34;p34) SF3A3/GNL2 (Iwakawa et al., 2013)  
 t(1;1)(p34;p34) SMAP2/MYCL (Iwakawa et al., 2013)  
 t(1;1)(p34;p34) ZMPSTE24/MFSD2A (Iwakawa et al., 2013)  
 t(1;1)(q21;q21) TXNIP/NOTCH2NL (Rudin et al., 2012)  
 t(1;1)(q25;q25) XPR1/TRMT1L (Iwakawa et al., 2013)  
 del(1)(q44q44) ZNF695/TFB2M (Rudin et al., 2012)  
 t(1;12)(p34;q24) TRIT1/EP400 (Iwakawa et al., 2013)  
 t(1;19)(p36;q13) UBE4B/TBCB (Iwakawa et al., 2013)  
 t(1;20)(p34;q11) BCL2L1/BMP8B (Iwakawa et al., 2013)  
 t(1;20)(p34;q11) BCL2L1/DEM1 (Iwakawa et al., 2013)  
 t(1;20)(p34;q11) BCL2L1/RIMS3 (Iwakawa et al., 2013)  
 t(1;20)(p34;q11) BCL2L1/RLF (Iwakawa et al., 2013)  
 t(1;20)(p34;q11) BCL2L1/ZNF643 (Iwakawa et al., 2013)  
 t(1;20)(p34;q11) BCL2L1/ZNF684 (Iwakawa et al., 2013)  
 t(1;20)(p34;q11) PPT1/BCL2L1 (Iwakawa et al., 2013)  
 t(1;20)(p34;q11) RLF/HM13 (Iwakawa et al., 2013)  
 t(2;5)(p22;q14) BIRC6/BHMT2 (Rudin et al., 2012)  
 t(2;6)(q31;p12) RCAN2/RAPGEF4 (Rudin et al., 2012)  
 t(2;12)(p23;p13) CACNA2D4/WDR43 (Campbell et al., 2008)  
 t(3;3)(p21;p21) NEK4/SFMBT1 (Rudin et al., 2012)

- t(3;3)(p21;q23) RASA2/NICN1 (Iwakawa et al., 2013)
- t(3;3)(q13;q22) STAG1/STXBP5L (Iwakawa et al., 2013)
- del(3)(q23;q23) SPSB4/ACPL2 (Rudin et al., 2012)
- t(3;3)(q23;q24) SLC25A36/PLSCR1 (Iwakawa et al., 2013)
- t(3;3)(q26;q26) GPR160/NCEH1 (Peifer et al., 2012)
- inv(3)(q26q27) DCUN1D1/ATP11B (Rudin et al., 2012)
- del(3)(q28q28) LPP/TPRG1 (Rudin et al., 2012)
- t(3;11)(p24;p15) NGLY1/CCKBR (Iwakawa et al., 2013)
- t(3;11)(p22;q14) DLEC1/ODZ4 (Iwakawa et al., 2013)
- t(3;11)(p21;p15) SFMBT1/AP2A2 (Iwakawa et al., 2013)
- t(3;12)(q13;p11) NAA50/MRPS35 (Rudin et al., 2012)
- t(3;16)(q21;p13) TXNDC11/RUVBL1 (Rudin et al., 2012)
- t(3;17)(q11;q21) NPEPPS/EPHA6 (Rudin et al., 2012)
- t(5;5)(q13;q13) NAIP/OCN (Iwakawa et al., 2013)
- t(5;5)(q31;q31) SKP1/CDKL3 (Rudin et al., 2012)
- t(5;5)(q31;q31) JADE2/UBE2B (Iwakawa et al., 2013)
- del(6)(q21q22) CEP85L/SCML4 (Rudin et al., 2012)
- t(6;8)(p21;p21) HMBOX1/ZFAND3 (Iwakawa et al., 2013)
- t(6;20)(p21;p12) CRLS1/KCNK17 (Iwakawa et al., 2013)
- del(7)(p21p21) ANKMY2/ISPD (Rudin et al., 2012)
- t(8;8)(q12;q24) PVT1/CHD7 (Campbell et al., 2008; Pleasance et al., 2010)
- t(8;8)(q12;q24) PVT1/CLVS1 (Iwakawa et al., 2013)
- inv(8)(q22q23) OXR1/COX6C (Rudin et al., 2012)
- inv(8)(q22q23) YWHAZ/OXR1 (Rudin et al., 2012)
- t(8;8)(q23;q23) NUDCD1/SYBU (Iwakawa et al., 2013)
- t(8;8)(q23;q24) CSMD3/MYC (Iwakawa et al., 2013)
- t(8;8)(q23;q24) PTK2/PKHD1L1 (Iwakawa et al., 2013)
- t(8;8)(q24;q24) PVT1/LY6H (Iwakawa et al., 2013)
- t(8;14)(p23;q22) AGPAT5/TXNDC16 (Rudin et al., 2012)
- t(8;14)(q24;q11) PVT1/CCNB1IP1 (Iwakawa et al., 2013)
- t(8;14)(q24;q11) PVT1/MYH7 (Iwakawa et al., 2013)
- t(8;14)(q24;q11) PVT1/SLC7A7 (Iwakawa et al., 2013)
- t(8;18)(q24;q12) PVT1/NOL4 (Iwakawa et al., 2013)
- t(9;9)(p24;p24) KANK1/DOCK8 (Rudin et al., 2012)
- t(9;9)(p24;p24) RIC1/JAK2 (Iwakawa et al., 2013)
- t(10;10)(p12;p12) WAC/GPR158 (Iwakawa et al., 2013)
- t(10;10)(p11;q21) CCDC7/UBE2D1 (Rudin et al., 2012)
- t(10;10)(q21;q21) CCDC6/CTNNA3 (Rudin et al., 2012)
- t(11;11)(p15;q23) ATP5L/TEAD1 (Iwakawa et al., 2013)
- t(11;11)(q14;q14) PICALM/CCDC81 (Iwakawa et al., 2013)
- t(11;11)(q14;q14) GAB2/NARS2 (Rudin et al., 2012)
- t(12;12)(p13;p13) ENO2/ACRBP (Iwakawa et al., 2013)
- inv(12)(p13p13) ERC1/ANO2 (Rudin et al., 2012)
- inv(12)(p13p13) C12orf4/CD9 (Rudin et al., 2012)
- del(12)(p13p13) ANO2/FBXL14 (Rudin et al., 2012)
- del(12)(q12q13) RPAP3/SCAF11 (Rudin et al., 2012)
- t(12;12)(q14;q21) PAWR/GNS (Iwakawa et al., 2013)
- t(12;12)(q23;q23) CHPT1/UTP20 (Rudin et al., 2012)
- t(12;12)(q24;q24) CIT/RFC5 (Iwakawa et al., 2013)
- t(12;12)(q24;q24) NCOR2/SCARB1 (Iwakawa et al., 2013)
- t(14;14)(q23;q23) MTHFD1/SYNE2 (Rudin et al., 2012)
- t(14;16)(q32;q12) SMEK1/HEATR3 (Iwakawa et al., 2013)
- t(15;15)(q21;q21) SPG11/SORD (Iwakawa et al., 2013)
- t(16;16)(p13;p13) CREBBP/RHBDF1 (Peifer et al., 2012; Iwakawa et al., 2013)
- t(16;16)(p13;p13) del(16)(p13p13) CREBBP/SLX4 (Pleasance et al., 2010)
- t(17;17)(p11;p13) MPRIP/TP53 (Peifer et al., 2012)
- t(17;17)(q25;q25) LRRC45/GCGR (Iwakawa et al., 2013)
- t(17;17)(q25;q25) FOXK2/HEXDC (Iwakawa et al., 2013)
- t(18;18)(p11;q12) TWSG1/PIK3C3 (Iwakawa et al., 2013)
- t(19;19)(p13;p13) NFIX/GATAD2A (Iwakawa et al., 2013)
- t(19;19)(p13;p13) DNMT2/ILF3 (Rudin et al., 2012)
- del(19)(p13p13) DNMT2/KCNN1 (Rudin et al., 2012)

inv(19)(p13p13) GIPC1/PKN1 (Rudin et al., 2012)  
 del(19)(q13q13) PPP1R37/KLC3 (Rudin et al., 2012)  
 t(20;20)(q11;q11) BCL2L1/HM13 (Iwakawa et al., 2013)  
 t(20;20)(q11;q11) TPX2/HM13 (Iwakawa et al., 2013)  
 inv(20)(q11q13) CEP250/DPM1 (Rudin et al., 2012)  
 inv(22)(q13q13) TTLL1/TSPO (Rudin et al., 2012)

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